HIPPOCAMPUS 17:709–722 (2007)

COMMENTARY

Functional Neuroanatomy of the Parahippocampal Region in the Rat: The Perirhinal and Postrhinal Cortices

Sharon C. Furtak,[1] Shau-Ming Wei,[1] Kara L. Agster,[2] and Rebecca D. Burwell[1,2]*

ABSTRACT: The parahippocampal region in the rodent brain includes the perirhinal, postrhinal, and entorhinal cortices, the presubiculum, and the parasubiculum. In recent years, the perirhinal and postrhinal cortices have been a focus in memory research because they supply highly processed, polymodal sensory information to the hippocampus, both directly and via the entorhinal cortex. Available evidence indicates that these cortices receive different complements of cortical information, which are then forwarded to the hippocampus via parallel pathways. Here we have summarized the cortical, subcortical, and hippocampal connections of the perirhinal and postrhinal cortices in order to provide further insight into the nature of the information that is processed by these regions prior to arriving in the hippocampus. As has been previously described, the cortical afferents of the rodent postrhinal cortex are dominated by structures known to be involved in the processing of visual and spatial information, whereas the cortical afferents of the perirhinal cortex result in remarkable convergence of polymodal sensory information. The two regions are also differentiated by their cortical efferents. The perirhinal cortex projects more strongly to piriform, frontal, and insular regions, whereas the postrhinal cortex projects preferentially to visual and visuospatial regions. The subcortical connections of the two regions provide further evidence that they have different functions. For example, the perirhinal cortex has strong reciprocal connections with the amygdala, which suggest involvement in processing affective stimuli. Subcortical input to the postrhinal cortex is dominated by projections from dorsal thalamic structures, particularly the lateral posterior nucleus. Although the perirhinal and postrhinal cortices are considered to contribute to the episodic memory system, many questions remain about their particular roles. A detailed description of the anatomical connections of the perirhinal and postrhinal cortices will permit the generation of new, anatomically guided, hypotheses about their role in episodic memory and other cognitive processes. © 2007 Wiley-Liss, Inc.

KEY WORDS: medial temporal lobe; afferent; efferent; neocortical; subcortical; hippocampus; parahippocampal

INTRODUCTION

Over the past decade, research on the neural circuitry of episodic memory has broadened from a focus on the hippocampal formation to include the surrounding parahippocampal region. In our terminology, the hippocampal system comprises the hippocampal formation (dentate gyrus, CA fields, and subiculum) and the parahippocampal region (the perirhinal (PER), postrhinal (POR), and entorhinal (EC) cortices together with the presubiculum and the parasubiculum). Brodmann's (1909) original description of the cortical regions surrounding the hippocampus included three cytoarchitectonically distinct cortices, areas 28, 35, and 36, also called the EC, PER, and ectorhinal cortices, respectively. Later anatomical work in the primate included two additional regions in the parahippocampal gyrus, termed TF and TH (Von Bonin and Bailey, 1947), now referred to, collectively, as the parahippocampal cortex. When applying this terminology to the rodent, Brodmann areas 28, 35, and 36 were translated into rodent EC and PER areas 35 and 36 (Rose, 1929; Krieg, 1946a), but there was no indication of a region comparable to the primate TF/TH. On the basis of the findings of a series of anatomical studies, Burwell and colleagues (Burwell et al., 1995; Burwell, 2001) redesignated the caudal portion of areas 35 and 36 as POR, a structure that exhibited considerable connectional homology with the parahippocampal cortex in the primate brain.

The cortical afferents of the POR and PER are dominated by visuospatial and polymodal input, respectively. This pattern of connections suggests that the POR, but not the PER, is involved in spatial functions. Experimental lesion studies, however, suggest that both regions may be involved in contextual learning. Deficits in contextual fear conditioning resulted from both pretraining and post-training lesions of either the PER (Corodimas and LeDoux, 1995; Bucci et al., 2000, 2002; Lindquist et al., 2004) or the POR (Bucci et al., 2000, 2002). Animals with PER or POR damage, which showed deficits in contextual learning, however, were not impaired in spatial learning in the Morris water maze (Burwell et al., 2004a; but see Liu and Bilkey, 2002; Winters et al., 2004). Thus, both the PER and the POR appear to contribute to contextual learning, but not to spatial navigation. Other approaches have provided evidence for a functional dissociation of the PER and POR. Norman and Eacott (2005) showed that performance on a novel object recognition task

[1] **Department of Psychology, Brown University, Providence, Rhode Island 02912;** [2] **Department of Neuroscience, Brown University, Providence, Rhode Island 02912**

Grant sponsor: NSF; Grant number: IBN 9875792; Grant sponsor: NSF; Grant number: IOB-0522220; Grant sponsor: NIH; Grant number: F31MH072144.

*Correspondence to: Rebecca D. Burwell, Brown University, 89 Waterman Street, Providence, RI 02912, USA. E-mail: rebecca_burwell@brown.edu

Accepted for publication 1 May 2007
DOI 10.1002/hipo.20314
Published online 29 June 2007 in Wiley InterScience (www.interscience.wiley.com).

was impaired when context was manipulated following ablation of the POR, but not the PER (see also Eacott et al., this issue).

Although the precise contribution of each region to contextual learning remains unclear, one hypothesis is that the PER and POR have separate but complimentary roles in processing contextual information. For example, the POR may have a role in monitoring and signaling changes in the spatial environment, and the PER may be necessary for encoding behaviorally relevant features of the environment. Such a role for the POR is consistent with the electrophysiology. The patterns of neuronal activity during spatial behavior indicate that the behavioral correlates of the POR firing differ from those of the hippocampus or dorsocaudal entorhinal cortex in the same tasks (Shapiro et al., 1997; Burwell and Hafeman, 2003; Fyhn et al., 2004). POR place cells reliably remap when distal spatial cues are manipulated. This finding is consistent with the notion that the POR contributes to contextual processing by detecting changes in the contextual environment (Bucci and Burwell, 2004). The idea that the POR has spatial functions that differ from those of the hippocampus is also consistent with evidence from humans with parahippocampal damage (Bohbot et al., 2000).

The notion that the PER may be necessary for encoding features of a spatial environment is consistent with a well-documented role in processing information about objects. Permanent and transient lesions of the PER significantly impair performance on object recognition tasks (Murray and Mishkin, 1998; Murray et al., 1998, 2000; Norman and Eacott, 2005; Winters et al., 2006). Perirhinal cells recorded from rodents and nonhuman primates demonstrate differential activity in response to familiar versus novel objects further implicating the PER in object memory (Zhu and Brown, 1995; Zhu et al., 1995; Holscher et al., 2003). More recent studies have provided evidence for a perirhinal contribution to the perceptual processing of complex stimuli. In rodents and nonhuman primates, perirhinal lesions result in a failure to make simultaneous or concurrent complex multifeature discriminations (Gaffan et al., 2000; Buckley et al., 2001; Eacott et al., 2001; Bussey et al., 2002). Studies of humans with perirhinal damage have also found deficits in complex multifeature discriminations (Barense et al., 2005; Lee et al., 2005).

It is clear from the review above that there are many outstanding questions about the role of the PER and POR in episodic memory and other cognitive processes. In the past, most neuroanatomically guided hypotheses about function of these regions have focused on the cortical connections. There are, however, substantial subcortical connections in addition to connectivity with the hippocampal formation and other parahippocampal regions. An understanding of the full complement of PER and POR connections can provide new insight into the neural bases of episodic memory.

NOMENCLATURE

In previous studies from our laboratory, the connections of the POR and PER were thoroughly examined across cortical, subcortical, and hippocampal system structures and substructures (Agster, 2007). The afferents and efferents were quantitatively assessed for 80 regions. Here we summarize the connections across all categories, specifically for the POR and the PER.

Postrhinal and Perirhinal Cortices

The borders of the POR and PER were defined in accordance with previous descriptions by Burwell and colleagues (Burwell et al., 1995; Burwell, 2000, 2001). Briefly, the POR is situated at the caudal pole of the rodent brain dorsal to the medial entorhinal area (MEA) and caudal to the PER (Fig. 1). It can be easily differentiated from the PER and MEA by the

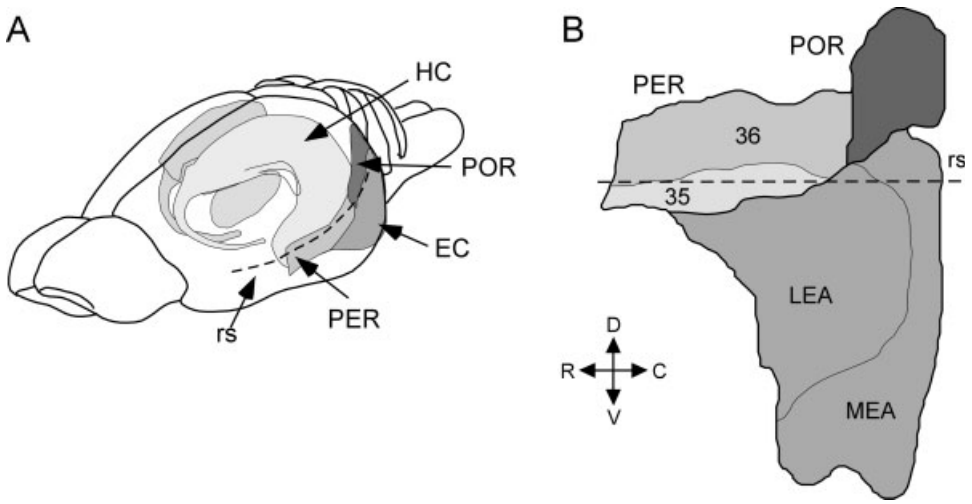

FIGURE 1. Location of the postrhinal and the perirhinal cortices in the rat brain. A: Lateral view of the rodent brain. Shading indicates the location of the hippocampal formation (HC), and the perirhinal (PER), entorhinal (EC), and postrhinal (POR) cortices. B: A two dimensional unfolded flat map of the PER, POR, and EC. Also shown are perirhinal areas 35 and 36, and the EC subdivisions, the lateral and the medial entorhinal areas (LEA and MEA). Panel A is adapted from (Witter and Amaral, 2004). Other abbreviations: c, caudal; d, dorsal; r, rostral; rs, rhinal sulcus; v, ventral.

presence of ectopic layer II cells. As an additional landmark, the POR first appears at the caudal level of the angular bundle. At more posterior levels, the POR is bordered dorsally by visual association cortex.

The rodent PER occupies both banks of the caudal half of the rhinal sulcus as well as a narrow strip of cortex immediately dorsal to it (Fig. 1A). The PER is located dorsal to the EC and rostral to the POR, as stated above. The PER can be differentiated from the EC by the presence of large, heart-shaped pyramidal cells in layer V. The rostral boundary of the PER is marked by the subcortical posterior limit of the claustrum. At its dorsal limit, the PER is bordered by the ventral temporal cortex (TEv). The PER comprises two regions, the dorsal area 36 and the ventral area 35, which can be distinguished by a number of cytoarchitectural characteristics, for example, layer thickness and cell density (Burwell et al., 1995; Burwell, 2001).

Cortical Regions

The cortical regions examined included the piriform cortex and subdivisions of the frontal, cingulate, insular, temporal, parietal, and occipital areas (Table 1). Aside from exceptions noted below, the cortical regional definitions are from Swanson (1998). The borders and cytoarchitecture of the piriform region have been well established (Rose, 1929; Krieg, 1946b; Haberly and Price, 1978). The rodent frontal cortex was subdivided into seven areas (Swanson, 1998). The borders and cytoarchitectonics described by Donoghue and Wise (1982) were used to define primary and supplementary motor regions. Other regions investigated included the prelimbic and infralimbic regions, and three orbital regions (medial, lateral, and ventrolateral orbital areas). The boundaries and nomenclature used to define these regions followed those set forth by Krettek and Price (1977). Agranular insular regions were divided into the dorsal, ventral, and posterior areas. The boundaries and defining criteria for these regions were adopted from Krettek and Price (1977). Two granular regions, gustatory and visceral cortices, were also investigated. The borders and cytoarchitectonics of these regions were taken from Swanson (1998).

Borders and nomenclature for ventral temporal and auditory areas were adapted from Swanson (1998). Dorsal and primary auditory regions were combined in anatomical analysis. Additionally, a ventral auditory region was investigated. Cingulate regions were divided into the dorsal and ventral anterior cingulate (Krettek and Price, 1977) and the dorsal and ventral retrosplenial regions (Krettek and Price, 1977; Vogt and Miller, 1983).

Parietal regions were divided into somatosensory and posterior areas. For the borders and nomenclature of primary and supplementary somatosensory regions we followed (Chapin and Lin, 1984). The posterior parietal region was initially defined by Krieg (1946a), but was modified by Swanson (1992). Two visual association regions were examined, a lateral and a medial. Borders for these regions were adapted by Swanson (1992) from Paxinos and Watson (1986).

TABLE 1.

List of Anatomical Regions Analyzed

Groups	Regions included in summary
Cortical	
Piriform	Not subdivided
Frontal	Primary motor, supplementary motor, prelimbic, infralimbic, medial orbital, lateral orbital, ventrolateral orbital
Insular	Dorsal agranular insular, ventral agranular insular, posterior agranular insular, gustatory, visceral
Temporal	Primary auditory cortex, secondary auditory cortex, ventral temporal association cortex
Cingulate	Dorsal anterior cingulate, ventral anterior cingulate, dorsal retrosplenial, ventral retrosplenial
Parietal	Primary somatosensory, supplementary somatosensory, posterior parietal
Occipital	Primary visual, medial visual association, lateral visual association
Subcortical	
Olfactory	Anterior olfactory nucleus, olfactory tubercle, piriform transition area, endopirifom, taenia tecta
Claustrum	Not subdivided
Amygdala	Lateral nucleus, basolateral nucleus, basomedial nucleaus, central nucleus, olfactory amygdala
Septum	Lateral septum, medial septum, posterior septum, bed nucleus of the stria terminalis
Basal ganglia	Caudate putamen, nucleus accumbens, globus pallidus, substantia innominata, substantia nigra-ventral tegmental area
Thalamus	Dorsal anterior group, dorsal lateral group, dorsal midline group, dorsal medial group, dorsal ventral group, epithalamus, intralaminar nuclei, reticular nucleus, lateral geniculate, medial geniculate, zona incerta, ventral lateral group
Hypothalamus	Periventricular zone, lateral zone, medial zone, mammillary bodies
Hippocampal system	
Hippocampal formation	Dentate gyrus, Fields CA3, CA2, CA1, subiculum
Parahippocampal region	Perirhinal cortex, postrhinal cortex, entorhinal cortex, presubiculum, parasubiculum

Subcortical Regions

Subcortical areas investigated included olfactory structures, the claustrum, and nuclei in the amygdala, septum, basal ganglia, thalamus, and hypothalamus. The dopaminergic cell groups within the substantia nigra and ventral tegmental areas were included. In general, we followed the nomenclature and definitions of subcortical structures proposed by Swanson (1992).

Olfactory areas examined included the olfactory tubercle, anterior olfactory nucleus, piriform transition area, endopiriform, and taenia tecta (Table 1). The claustrum was also included. The borders from Swanson (1992) were adapted from Witter et al., (1988). The amygdala was subdivided into five regions: the lateral, basolateral, basomedial, and central nuclei, and the olfactory amygdala. The olfactory amygdala included the structures that receive direct input from the olfactory bulb or the accessory olfactory bulb, including the nucleus of the lateral olfactory tract, the bed nucleus of the accessory olfactory tract, the anterior amygdaloid area, the medial nucleus, and the cortical nucleus. Boundaries and nomenclature associated with these regions were adopted from Swanson (1992) and Krettek and Price (1978). The septal area included four subregions for anatomical analysis. These regions included the lateral, medial, and posterior septal nuclei, and the bed nucleus of the stria terminalis. The basal ganglia regions included the caudate putamen, nucleus accumbens and fundus of the striatum, globus pallidus, and the substantia innominata. For convenience, the substantia nigra and ventral tegmental areas were grouped with basal ganglia structures.

In order to simplify the analysis, the thalamic nuclei were grouped into a set of dorsal thalamic structures and a set of ventral thalamic structures. In general, the boundaries and grouping criteria used were taken from Swanson (1992) and Jones (1985). Five groups of dorsal thalamic structures were examined. The lateral and medial habenula were combined into the epithalamus. The remaining dorsal groups included the dorsal midline, anterior, medial, lateral, and ventral groups. The dorsal midline thalamic group comprised the paraventricular nucleus, the parataenial nucleus, and the nucleus reuniens. The dorsal anterior thalamic group comprised the anteroventral, anteromedial, anterodorsal, interanteromedial, interanterodorsal, and lateral dorsal nuclei of the thalamus. The dorsal medial thalamic group included the mediodorsal nucleus, the submedial thalamic nuclei, and the perireuniens nucleus. Nuclei included in the dorsal lateral thalamic group included the suprageniculate and lateral posterior nuclei, the posterior limiting nucleus, and the posterior complex of the thalamus. Finally, the dorsal ventral thalamic group included the ventral anterior lateral complex, the ventral posterior complex of the dorsal thalamus, and the ventral medial nucleus.

The ventral thalamic regions investigated included the lateral and medial geniculate complexes, the intralaminar nucleus, the reticular nucleus, the zona incerta, and a combination of structures that we have termed the ventrolateral thalamic group (VLTH). The lateral geniculate complex included the dorsal and ventral portions of the lateral geniculate complex and the intergeniculate leaflet. The VLTH included the subthalamic nucleus, the perifasicular nucleus, and the peripeduncular nucleus.

Finally, the hypothalamic nuclei were grouped into four larger regions to facilitate analysis. Borders and nomenclature of these areas were taken from Swanson (1992). Areas investigated included the periventricular zone, the medial zone, the lateral zone, and the mammillary bodies. The periventricular zone comprised the periventricular, anteroventral, anterior, intermediate, and posterior periventricular hypothalamic nuclei. Additionally, the vascular organ of the lamina terminalis, the suprachiasmatic and median pre-optic nuclei, the pre-optic periventricular nucleus, and the arcuate nucleus were combined into the periventricular zone. Structures within the medial zone included the medial, anterodorsal, anteroventral, posterodorsal pre-optic, the parastrial, and the suprachiasmatic nuclei, as well as the retrochiasmatic area, the subparaventricular zone, the anterior hypothalamic area, and the tuberal area of the hypothalamus. The lateral zone included the lateral pre-optic area and the lateral hypothalamic area. Finally, the mammillary bodies included the dorsal, medial, and lateral mammillary nuclei, the tuberomammillary nucleus, and the supramammillary nucleus.

Hippocampal System

For the hippocampal system, the connections with all structures in the hippocampal formation and the parahippocampal region were assessed. Structures included in the hippocampal formation were the CA fields of the hippocampus proper (CA1, CA2, and CA3), the dentate gyrus, and the subiculum. These regions are heavily interconnected, and can be distinguished structurally from the parahippocampal region in that they contain only three layers (Witter et al., 2000). Additionally, all regions within the hippocampal formation were divided into dorsal and ventral subfields for anatomical analysis.

The parahippocampal region comprises the PER, POR, EC, presubiculum, and parasubiculum (Scharfman et al., 2000). The presubiculum included the most dorsal extent, sometimes termed the postsubiculum. All areas within the parahippocampal region have six layers, thereby distinguishing them from the associated hippocampal formation (Witter et al., 2000). The presubiculum was further subdivided into a dorsal and ventral portion. The parasubiculum was subdivided along the rostrocaudal extent of the region into the rostral and caudal portions. The EC was subdivided into the lateral entorhinal area (LEA) and MEA (Insausti et al., 1997).

OVERVIEW OF THE CONNECTIONS

For this report, we have reanalyzed and summarized the results of a prior series of neuroanatomical experiments (Burwell and Amaral, 1998a,b; Agster, 2007) in order to specifically address the afferents and efferents of the PER and POR. For afferents, retrograde tract tracer injections were placed into either the PER, POR, or EC. Total numbers of retrogradely-labeled cells in each of the projection regions were estimated. Methods for counting labeled cells in cortical regions were previously described (Burwell and Amaral, 1998a). Methods for

TABLE 2.

Cortical Afferents of the POR and PER: Percent Retrogradely-labeled Cells[a]

			Area 36				Area 35		
Origins	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	mid-rc	caudal
Piriform	0.3	5.5	13.2	9.1	0.0	34.2	44.5	23.9	46.0
Frontal	4.3	8.0	10.9	4.9	6.8	12.1	8.0	13.8	11.3
Insular	1.0	15.8	19.3	11.1	3.6	30.2	33.5	26.5	24.4
Temporal	22.8	56.0	40.1	67.2	49.6	14.5	5.2	26.4	11.9
Cingulate	15.4	2.3	1.9	2.3	3.3	1.2	0.7	0.6	2.2
Parietal	10.0	6.3	9.7	4.1	8.8	6.8	7.9	7.4	3.0
Occipital	46.2	6.1	4.8	1.4	27.9	1.0	0.2	1.3	1.1
Total (%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*

Numbers represent the mean percent of the total number of retrogradely labeled cells in the originating cortical regions arising from injections in postrhinal (POR) and perirhinal (PER) areas 36 and 35.

[a]Note that labeled cells in cortical regions accounted for 63% of all labeled cells in POR, 50% for area 36, and 53% for area 35. See text for details.

the subcortical and hippocampal structures were similar, with the exception that counting of labeled cells was automated (Neurolucida, MBF Bioscience, Williston, VT). The percentage of total labeled cells for each group of structures (cortical, subcortical, and hippocampal regions) was calculated as the number of cells labeled in the projection structure divided by the total labeled cells for the group. The percentage measure was chosen for the purposes of this report because it best reflects the impact of the afferent structures on the PER and POR.

For the efferent projections, anterograde tract tracers were placed into the PER, POR, and EC, and the density of fiber labeling was examined (Burwell and Amaral, 1998a,b; Agster, 2007). An index of fiber labeling was constructed as follows: The area of a target structure in a series of coronal sections was divided into voxels of a specified area. The density of fiber labeling was then examined against a set of six standards and rated on a scale of 0 to 6, such that 0 indicated no label present and a score of 6 indicated very dense fiber labeling. Ratings were assessed for each voxel for a series of coronal sections at 0.3 mm intervals along the rostrocaudal axis. The ratings for each voxel for a particular region were then summed to obtain an index of fiber labeling that was weighted for the volume of the structure (Agster, 2007). It should be noted that the density of fiber labeling was not normalized across cases for these analyses. This fiber index was chosen for the purposes of this summary because it best represents the impact of the POR, PER, and EC on their efferent targets. See Kerr et al. (this issue) for a discussion of the strengths and limitations of this approach to quantifying projection strength.

CORTICAL CONNECTIONS OF THE POSTRHINAL CORTEX

Afferent input to the POR arises primarily from cortical regions. In fact, just under two thirds of the total projections to the POR originate in cortical areas based on retrogradely-labeled cells. As shown in Table 2, the strongest cortical input to the POR originates from occipital regions, accounting for about half of the total POR cortical input in terms of the percentages of labeled cells (Table 2; Burwell and Amaral, 1998a). The heaviest inputs arise in the lateral and the medial visual association regions, but there is also substantial input from primary visual cortex. The POR also receives a moderate input from temporal regions, contributing roughly a quarter of cortical input (Burwell and Amaral, 1998a). The majority of these afferents arise from ventral temporal cortex (Fig. 2A). A much smaller proportion of input arises from auditory regions within the temporal cortex.

Additionally, cingulate regions provide a moderate proportion of input to the POR (Burwell and Amaral, 1998a). This input, which is highly reciprocal, arises almost entirely from dorsal retrosplenial regions (Figs. 2A,B). Posterior parietal cortex, in particular the caudal limb, provides a substantial input to the POR. This projection from the posterior parietal cortex to the POR exhibits strong reciprocity from the POR. The POR receives little input from frontal regions, accounting for only 4% of the total cortical input to the POR (Burwell and Amaral, 1998a). The majority of frontal afferents arise from supplementary motor areas. Very few projections to the POR arise from either the piriform cortex or insular regions, which provide less than one percent of the total cortical input to the POR (Burwell and Amaral, 1998a). Overall, the cortical inputs to the POR are dominated by areas involved in visual and spatial function.

Generally, the topography of the POR efferent connections displays strong reciprocity with the pattern of its afferent projections. The POR efferent projections are heaviest to the occipital region followed by strong projections to the temporal and cingulate regions (Table 3). The majority of projections from the POR to the occipital regions concentrate in the medial visual association cortex (Fig. 2B; Agster, 2007). Similar to the pattern of afferent projections from the temporal cortex, the POR projects strongly to the ventral temporal cortex (Fig. 2B).

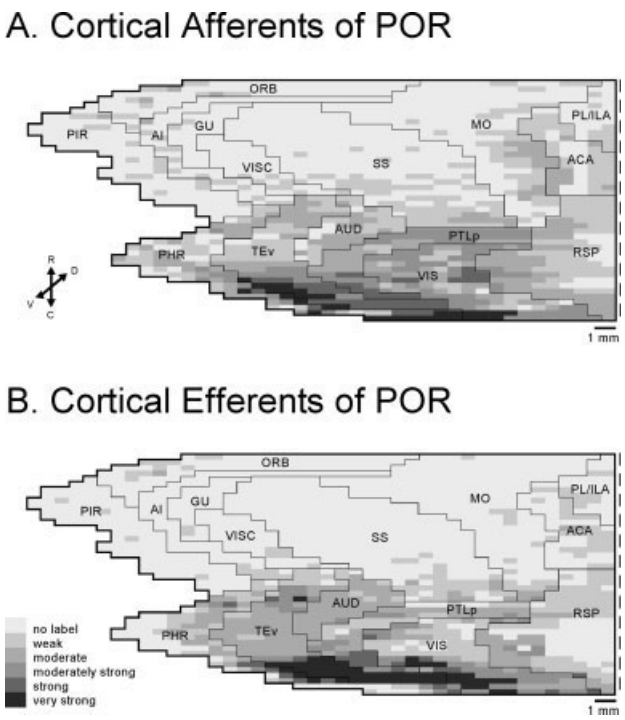

FIGURE 2. Unfolded template maps showing the topography of the cortical connections of the postrhinal cortex (POR). A: This map is adapted from a representative retrograde tract tracer case in the POR. Levels of grey represent densities of labeled cells resulting from an injection in the POR. B: This unfolded map is a composite of two representative anterograde tract tracer cases showing the density of fiber labeling in cortical regions resulting from injections in the POR. Abbreviations for this and the next figure: ACA, anterior cingulate; AI, agranular insular; AUD, auditory cortex; GU, gustatory; MO, motor cortex; ORB, orbital frontal regions; PIR, piriform cortex; PHR, parahippocampal region; PL/ILA, prelimbic/infralimbic areas; PTLp, posterior parietal, RSP, retrosplenial; SS, somatosensory cortex; TEv, ventral temporal association cortex; VISC, visceral cortex; VIS, visual cortex.

Overall, projections to the temporal cortex represent the second greatest density of efferent labeling within cortical regions following injections into the POR. The POR also has a moderate projection that terminates in dorsal auditory areas of the temporal cortex thought to be primary auditory cortex (Agster, 2007). Return projections to frontal regions are moderate and terminate in supplementary and primary motor cortices. Posterior parietal cortex is the main parietal target of the POR, but a smaller projection terminates in primary somatosensory regions (Fig. 2B; Agster, 2007). Projections from the POR to insular regions and the piriform cortex represent a small portion of the cortical efferents.

CORTICAL CONNECTIONS OF AREA 36 OF THE PERIRHINAL CORTEX

Based on percentages of labeled cells following retrograde tract tracer injections, about half of all afferent connections to area 36 of the PER arise in cortical structures. The temporal cortex provides the heaviest input to area 36, accounting for roughly half of the cortical input (Table 2; Burwell and Amaral, 1998a). The majority of the substantial projection from the temporal cortex originates in ventral temporal cortex, which is anatomically adjacent to area 36 and provides auditory, olfactory, and visual sensory information (Fig. 3A). Area 36 also receives input from primary and secondary auditory regions within the temporal cortex. The projection from the temporal cortex terminates in all levels of area 36, with the mid-rostrocaudal level receiving the most robust inputs. In addition, there is a moderate projection from insular regions that preferentially targets the rostral part of area 36, contributing about one fifth of the input (Burwell and Amaral, 1998a; Burwell, 2001). Although the occipital cortex provides a weak input to area 36 on average, it provides nearly one third of all cortical input to caudal area 36. A large portion of the projection from the occipital cortex to caudal area 36 arises in the visual association regions.

Area 36 has substantial efferent connections that innervate parietal, temporal, and frontal areas (Table 3 and Fig. 3C). The strongest efferent projection from area 36 arises in the rostral part of the region and terminates in somatosensory cortex.

TABLE 3.

Cortical Efferents of the POR and PER: Index of Fiber Labeling

			Area 36				Area 35	
Terminations	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	caudal
Piriform	3.3	22.6	10.4	17.2	45.7	17.6	26.3	8.9
Frontal	7.0	30.9	69.9	25.9	1.8	26.5	37.0	16.0
Insular	1.8	16.7	22.2	22.0	0.5	22.0	33.8	10.1
Temporal	25.7	30.4	21.0	37.1	26.4	13.5	5.6	21.4
Cingulate	22.4	5.9	5.4	5.6	7.1	4.1	3.7	4.6
Parietal	20.5	31.9	95.8	9.8	12.1	20.7	22.9	18.5
Occipital	47.2	7.8	6.0	3.9	17.2	5.6	1.0	10.3

Numbers represent indexes of fiber labeling in terminal cortical regions arising from anterograde tracer injections of postrhinal (POR) cortex and perirhinal (PER) areas 36 and 35. Density of fiber labeling was rated and then normalized by the volume of the terminal structure. See text for details.

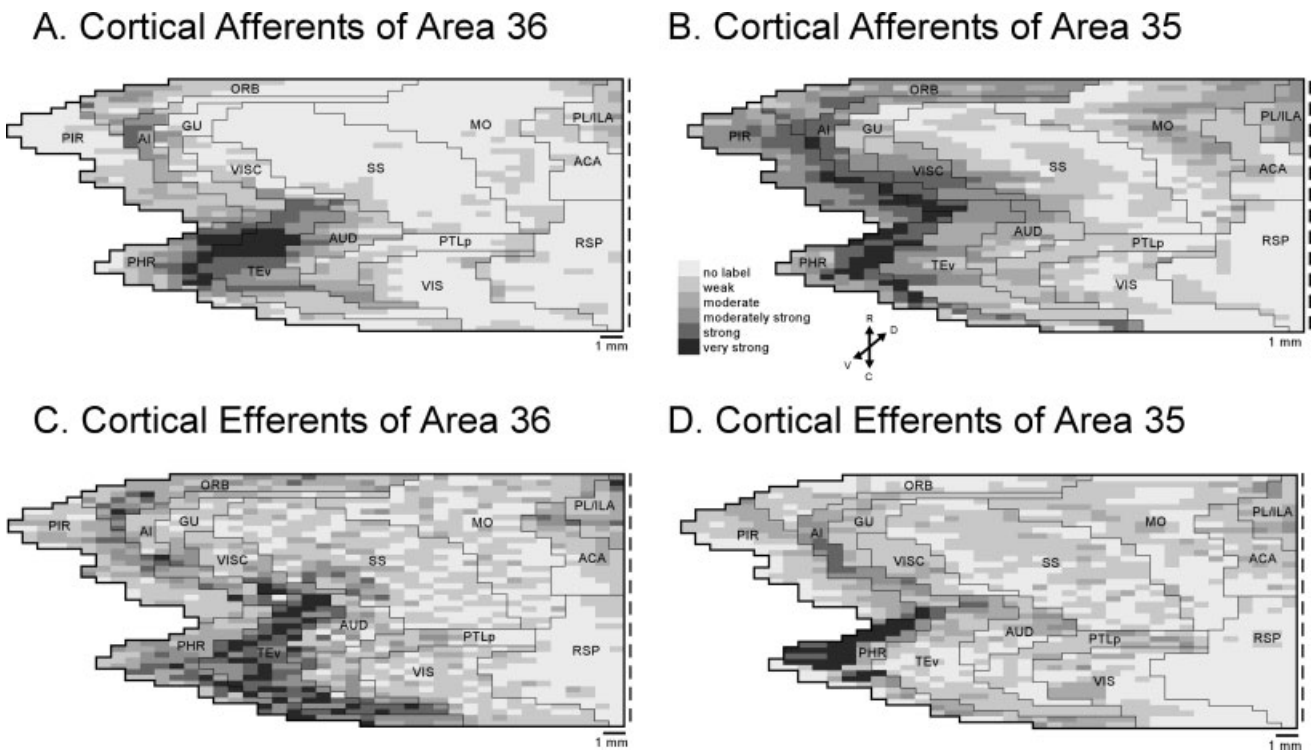

FIGURE 3. Unfolded template maps showing the topography of the cortical connections of the perirhinal (PER) areas 36 and 35. A: This map is adapted from a representative retrograde tract tracer case with an injection in area 36 of the perirhinal cortex. Levels of grey represent densities of labeled cells resulting from the injection. B: This map represents a retrograde tract tracer case in which the injection site was in perirhinal area 35. Levels of grey represent densities of labeled cells resulting from the injection. C: This unfolded map is a composite of three representative anterograde tract tracer cases showing the density of fiber labeling in cortical regions resulting from injections in rostral, mid-rostrocaudal, and caudal area 36. D: This unfolded map is a composite of two representative anterograde tract tracer cases showing the density of fiber labeling in cortical regions resulting from injections in rostral and caudal area 35. For abbreviations, see legend for Figure 2.

Rostral area 36 substantially contributes to projections that terminate in frontal regions. In addition, the mid-rostrocaudal and caudal levels of area 36 strongly project to temporal regions and the piriform cortex, respectively. The projections to the cingulate and occipital regions are weak.

CORTICAL CONNECTIONS OF AREA 35 OF THE PERIRHINAL CORTEX

Percentages of labeled cells resulting from retrograde tract tracer injections in area 35 suggest that approximately one half of all afferent connections to area 35 arise from cortical regions. Area 35 receives strong afferent projections from both the piriform cortex and insular regions, with each contributing approximately one third of the cortical inputs (Table 2; Burwell and Amaral, 1998a). The projection from the piriform cortex largely terminates in the rostral and caudal area 35, whereas insular regions innervate the entire rostrocaudal extent of area 35 (Fig. 3B). Area 35 receives fewer cortical afferents from the temporal cortex as compared to area 36. Temporal cortex afferents preferentially terminate in the mid-rostrocaudal level of area 35, accounting for roughly one quarter of cortical input to this level (Burwell and Amaral, 1998a).

Overall, area 35 projections to cortical structures are weaker than those of area 36. The strongest projection arises from area 35 and terminates in frontal areas (Table 3). The next strongest projection is to insular areas. That projection arises in rostral area 35 and is distributed to all insular regions. The frontal projection from rostral area 35 terminates largely in the supplementary and primary motor regions. Area 35 also has a moderate efferent connection to the parietal cortex (Fig. 3D).

SUBCORTICAL CONNECTIONS OF THE POSTRHINAL CORTEX

The subcortical afferents of the POR are weaker than the cortical and hippocampal afferents. Subcortical structures provide less than 15% of the total input to POR as assessed by the number of retrogradely-labeled cells. The dorsal thalamic nuclei dominate the subcortical input to the POR, representing over half of the total subcortical innervation (Table 4). The strongest of these afferent projections from the dorsal thalamus originates in the dorsal lateral group, which contribute to

TABLE 4.

Subcortical Afferents of the POR and PER: Percent Retrogradely-labeled Cells[a]

			Area 36				Area 35		
Origins	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	mid-rc	caudal
Olfactory	1.2	3.9	8.6	1.8	1.7	30.3	39.4	27.9	17.0
Claustrum	20.5	5.5	9.4	1.7	10.8	20.3	23.4	17.3	20.2
Amygdala	3.4	42.4	42.6	53.0	20.9	25.0	17.2	23.3	44.1
Septal nuclei	2.5	0.2	0.1	0.2	0.6	1.1	0.9	1.2	1.1
Basal ganglia	1.2	2.2	2.4	1.8	2.9	2.1	2.2	2.3	1.5
Dorsal thalamus	56.2	25.8	17.0	22.0	52.8	12.5	11.6	13.2	12.7
Ventral thalamus	11.3	18.4	17.4	18.2	8.3	7.2	4.3	12.8	2.0
Hypothalamus	3.8	1.7	2.5	1.3	2.1	1.6	1.2	2.1	1.4
Total (%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*

Numbers represent the mean percent of the total number of retrogradely labeled cells in the originating in subcortical regions arising from injections in postrhinal cortex (POR) and perirhinal (PER) areas 36 and 35.

[a]Note that labeled cells in subcortical regions accounted for 14% of all labeled cells for the POR, 39% for area 36, and 36% for area 35. See text for details.

approximately half of the labeled cells in the dorsal thalamus (Agster, 2007). The claustrum provides the second densest subcortical innervation to the POR and accounts for roughly one fifth of the total subcortical input in percentages of labeled cells. The POR receives moderate afferent connections from the ventral thalamus. The intralaminar nuclei provide the vast majority of this input (Agster, 2007). Few afferent projections to the POR originate in the amygdala and basal ganglia. Of the few afferents from the amygdala to the POR, the lateral and basolateral nuclei provide the strongest inputs (Agster, 2007).

The strongest subcortical efferent projection from the POR terminates in the basal ganglia, with labeled fibers terminating almost exclusively in the tail of the caudate putamen (Agster, 2007). There are also moderately strong projections from the POR to the dorsal thalamus, followed by the ventral thalamus and amygdala (Table 5). Similar to the afferent connections with the dorsal thalamus, the strongest efferent fiber labeling is observed in the dorsal lateral and dorsal anterior groups (Agster, 2007). Efferent projections to the ventral thalamus are more widespread; however, labeled fibers are most frequently observed in the lateral geniculate and zona incerta. Moderate projections from the POR to the amygdala exist. These efferent projections from the POR to the amygdala terminate mostly in the lateral and basolateral nuclei. Other subcortical efferent projections that originate in the POR are quite weak.

SUBCORTICAL CONNECTIONS OF AREA 36 OF THE PERIRHINAL CORTEX

Subcortical structures contribute roughly one-third of the total afferent connections of area 36, as indicated by the percent of retrogradely-labeled cells. The principal subcortical

TABLE 5.

Subcortical Efferents of the POR and PER: Index of Fiber Labeling

			Area 36				Area 35	
Terminations	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	caudal
Olfactory	1.3	24.7	41.6	152.9	3.1	44.0	58.9	29.2
Claustrum	3.5	12.5	31.7	65.3	3.3	11.9	17.3	6.6
Amygdala	11.0	38.0	46.9	245.3	12.1	26.0	36.7	15.3
Septal nuclei	3.8	5.6	4.4	39.4	1.1	5.2	7.1	3.2
Basal ganglia	109.2	165.7	491.9	734.5	99.2	121.5	150.8	92.1
Dorsal thalamus	27.7	14.2	54.5	46.0	13.3	2.8	3.3	2.3
Ventral thalamus	13.4	8.3	27.5	34.7	4.3	2.2	3.2	1.1
Hypothalamus	1.3	4.4	9.4	24.6	1.5	1.0	1.0	1.0

Numbers represent indexes of fiber labeling in terminal subcortical regions arising from anterograde tracer injections in postrhinal cortex (POR) and perirhinal (PER) areas 36 and 35. Note that the fiber labeling index in larger structures, for example basal ganglia structures, will yield higher numbers. Density of fiber labeling was rated and then normalized by the volume of the terminal structure. See text for details.

afferent to area 36 arises from the amygdala and contributes to roughly half of the subcortical inputs (Table 4). The lateral nucleus of the amygdala contributes most heavily to this strong projection, which terminates largely in rostral area 36. In addition to the afferents that arise from the amygdala, both the dorsal and ventral thalamic nuclei provide moderate input to area 36. The dorsal thalamus strongly innervates caudal levels of area 36, contributing slightly more than half of the subcortical input to this level. The largest projection from the dorsal thalamus to all rostrocaudal levels within area 36 originates in the lateral group. In contrast to the dorsal thalamus, the ventral thalamic input terminates in more rostral levels of area 36. The medial geniculate nucleus provides the strongest ventral thalamic input to area 36. The septal nuclei, the basal ganglia and the hypothalamus provide weak input as indicated by percentages of labeled cells in those areas.

Area 36 of the PER provides widespread inputs to subcortical structures. Most are modest, with the exception of the basal ganglia projection; a very heavy projection targets the caudate putamen (Table 5). It should be noted, however, that the large volume of the basal ganglia structures will result in larger fiber labeling indexes. In addition, there is a strong efferent projection from area 36 that terminates in the amygdala. The projection largely originates in the mid-rostrocaudal portion of area 36 and, interestingly, terminates throughout the amygdala nuclei. There are strong projections from the mid-rostrocaudal division of area 36 to the olfactory area. Moderate projections from the PER target the dorsal lateral group of the dorsal thalamus and the zona incerta of the ventral thalamus.

SUBCORTICAL CONNECTIONS OF AREA 35 OF THE PERIRHINAL CORTEX

Based on the percentage of retrogradely-labeled cells, subcortical afferents contribute almost one half of total input to area 35 of the PER. The strongest projection to area 35 originates in the olfactory areas, accounting for roughly one third of all subcortical inputs, followed closely by the amygdala and the claustrum (Table 4). Most of the olfactory inputs arise from the endopiriform and the piriform transition areas, and both subregions most heavily innervate the rostral level of area 35. The amygdala, the lateral nucleus in particular, strongly projects to caudal area 35 and provides slightly less than half of subcortical inputs to this level. In contrast to the amygdala, the claustrum contributes input to all rostrocaudal levels of area 35 (Table 4). Area 35 receives a moderate projection from the dorsal thalamus that mainly arises from the midline group nuclei. The ventral thalamus along with the septal nuclei, the basal ganglia, and the hypothalamus, provide little input to area 35 (Table 4).

Overall, the subcortical efferents of area 35 are weak. The exception is the very strong projection that terminates in the basal ganglia (Table 5). Interestingly, even though the afferent input from the basal ganglia to area 35 is weak, the reciprocal efferent projection is strong, especially to the nucleus accumbens. The next largest projection is to olfactory areas. The projection terminates in all olfactory structures, but the projection to the accessory olfactory nucleus is weak. The projection from rostral area 35 to the amygdala is also moderately strong. Within the amygdala, the basomedial nucleus is the main target of area 35. The claustrum receives a moderate projection from area 35, specifically from the rostral level. Area 35 projections to the thalamus and the hypothalamus are weak (Table 5).

HIPPOCAMPAL SYSTEM CONNECTIONS OF THE POSTRHINAL CORTEX

The hippocampal system connections to the POR are relatively weak; however, they still substantially stronger than the subcortical afferents of the POR. Approximately one quarter of the total input to the POR originates in the hippocampal system as assessed by percentages of retrogradely-labeled cells (Fig. 2A). The majority of these retrogradely-labeled cells were located in parahippocampal structures (Table 6). The PER and the caudal parasubiculum provide the strongest inputs (Agster, 2007). Area 36 provides the heaviest afferent projection from the PER to the POR (Burwell and Amaral, 1998a). The EC also provides a substantial input to the POR (Fig. 2A; Burwell and Amaral, 1998a). The overall contribution of the hippocampal formation to the input of the POR is much weaker than the parahippocampal contribution (Agster, 2007). However, the dorsal hippocampal formation does provide a moderate afferent projection to the POR, accounting for approximately ten percent of the total hippocampal system input. The majority of this connection originates in the CA1 (Agster, 2007).

The largest efferent projections from the POR terminate in the parahippocampal region (Tables 3, 5, and 7). These projections terminate primarily in the PER and EC (Fig. 2B and Table 7; Burwell and Amaral, 1998a). Fiber labeling following POR anterograde tracer injections is dense in both areas 35 and 36, as well as the EC (Burwell and Amaral, 1998a). In contrast, substantially fewer efferent projections from the POR terminate in the presubiculum and parasubiculum (Agster, 2007). The presubicular projection terminates preferentially in the most dorsal portion of the presubiculum, sometimes called the postsubiculum. Finally, output to the dorsal and the ventral hippocampal formation is weak.

HIPPOCAMPAL CONNECTIONS OF AREA 36 OF THE PERIRHINAL CORTEX

Overall, the hippocampal system projects weakly to area 36 of the PER. Of this small afferent projection, the parahippocampal region provides by far the heaviest input, which terminates throughout the rostrocaudal extent of area 36 (Table 6 and Fig. 3A). The POR and EC provide the majority of the parahippocampal input to area 36 (Table 6). The connections from POR largely innervate the mid-rostrocaudal and caudal

TABLE 6.

Hippocampal Afferents of the POR and PER: Percent Retrogradely-labeled Cells[a]

			Area 36				Area 35		
Origins	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	mid-rc	caudal
Dorsal HC	*10.3*	*1.0*	*0.5*	*1.4*	*0.9*	*7.1*	*4.2*	*9.8*	*7.5*
DG/CA3	0.1	0.1	0.2	0.1	0.0	0.1	0.0	0.3	0.1
CA2/CA1	7.4	0.7	0.1	1.1	0.4	4.5	3.6	4.7	5.9
SUBd	2.8	0.2	0.2	0.2	0.5	2.5	0.6	4.7	1.5
Ventral HC	*4.5*	*17.3*	*17.6*	*15.3*	*22.7*	*11.2*	*3.7*	*23.0*	*8.4*
DG/CA3	0.0	0.5	0.0	1.0	0.0	0.6	0.0	2.1	0.0
CA2/CA1	2.9	13.5	13.7	12.0	17.9	8.0	3.2	15.1	6.6
SUBv	1.6	3.3	3.9	2.3	4.7	2.6	0.5	5.7	1.8
ParaHC Region	*85.1*	*81.7*	*81.9*	*83.3*	*76.5*	*81.7*	*92.1*	*67.2*	*84.2*
Presubiculum	16.3	2.1	0.34	2.8	3.0	0.8	0.2	2.0	0.5
Parasubiculum	22.2	3.2	3.0	1.0	11.5	1.9	0.7	3.7	2.3
PER/POR	28.4	42.3	28.2	49.2	49.9	6.3	2.5	5.9	14.0
Entorhinal	18.3	34.1	50.4	30.3	12.1	72.7	88.8	55.6	67.4
Total (%)	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*	*100.0*

Numbers represent the mean percent of the total number of retrogradely labeled cells in the originating cortical regions arising from injections in postrhinal (POR) cortex and perirhinal (PER) areas 36 and 35.

[a]Note that labeled cells in hippocampal and parahippocampal structures accounted for 23% of all labeled cells in the POR, 12% for area 36, and 10% for area 35. See text for details.

levels of area 36 whereas EC projections terminate preferentially in rostral area 36. Slightly less than one fifth of area 36 input arises from the ventral HC. This projection originates primarily in field CA1. In contrast, the dorsal division of the hippocampus provides a negligible input to area 36. These findings are inconsistent with previously reported electrophysiology (Kloosterman et al., 2004). It may be, however, that the CA1 input to area 35 accounts for the dorsal hippocampal connections in prior studies.

Area 36 provides only modest input to the hippocampal formation (Table 7). The projection targets field CA1 and the subiculum in both dorsal and ventral hippocampus. In contrast, area 36 provides very strong input to the EC (Table 7 and Fig. 3C). The projection arises in all rostrocaudal levels of area 36.

TABLE 7.

Hippocampal Efferents of the POR and PER: Index of Fiber Labeling

			Area 36				Area 35	
Terminations	POR average	Area 36 average	rostral	mid-rc	caudal	Area 35 average	rostral	caudal
Dorsal HC								
DG/CA3	3.6	0.1	0.0	0.9	0.0	0.0	0.0	0.0
CA2/CA1	2.1	0.6	0.0	3.0	2.0	0.5	0.0	1.0
SUBd	2.1	0.2	0.0	0.0	1.3	1.7	0.5	2.8
Ventral HC								
DG/CA3	0.3	0.1	0.0	0.4	0.0	0.0	0.0	0.0
CA2/CA1	0.2	1.2	0.0	9.0	0.3	0.4	0.4	0.4
SUBv	1.1	0.9	0.0	2.9	4.5	5.5	2.7	8.4
ParaHC Region								
Presubiculum	8.9	0.5	0.0	3.0	0.8	0.5	0.2	0.8
Parasubiculum	3.4	0.1	0.0	1.0	0.0	0.2	0.0	0.3
PER/POR	172.9	29.0	11.4	32.5	46.9	17.4	0.4	34.3
Entorhinal	166.6	107.7	87.5	118.3	94.7	191.0	178.4	203.7

Numbers represent indexes of fiber labeling in terminal hippocampal regions arising from anterograde tracer injections in the postrhinal cortex (POR) and perirhinal (PER) areas 36 and 35. Density of fiber labeling was rated and then normalized by the volume of the terminal structure. See text for details.

In addition, the mid-rostrocaudal and caudal levels of area 36 provide moderate input to the POR.

HIPPOCAMPAL CONNECTIONS OF AREA 35 OF THE PERIRHINAL CORTEX

Similar to area 36, area 35 of the PER receives a very small portion of its input from the hippocampal system. Input to area 35 originates in the parahippocampal region (Table 6 and Fig. 3B). In particular, EC accounts for roughly three-quarters of the hippocampal system input, which terminates in all rostrocaudal levels of area 35 (Table 6). In addition, caudal area 35 receives a modest input from the POR. Area 35 receives modest input from the dorsal and ventral HC. The HC input arises largely from field CA1 and to a lesser extent, the subiculum, and terminates in caudal area 35 (Table 6). The input from ventral HC is stronger than the input from dorsal HC.

Heavy efferent projections from area 35 terminate almost exclusively in the EC (Table 7 and Fig. 3D). The projection to the EC is very heavy and arises from the entire rostrocaudal extent of area 35. The POR, in contrast, receives a moderate projection that originates in caudal area 35. Area 35 projects to the subiculum, and the projection to ventral subiculum is stronger than to dorsal subiculum.

CONCLUSIONS

The POR has strong reciprocal connections with the caudal part of the ventral temporal cortex, the posterior parietal cortex, dorsal retrosplenial cortex, and visual association areas. These are all regions that have been implicated in visuospatial functions (Vaudano et al., 1991; Shi and Cassell, 1997; Broussard et al., 2006). The pattern of subcortical connections of the POR also supports a strong bias towards visual information processing. Dense reciprocal connections exist between the POR and the lateral posterior nucleus of the thalamus. The lateral posterior nucleus is the rodent homolog of the primate pulvinar nucleus, a region implicated in visual attention (Posner and Petersen, 1990). Additionally, though not formally quantified, we observed labeled fibers in the superior colliculus following anterograde tracer injections in the POR. Finally, the POR is heavily connected with the dorsal hippocampal formation, a region of the hippocampus especially biased towards spatial processing (Moser et al., 1993, 1995; Jung et al., 1994). The POR receives very little input from the nonvisual sensory modalities, a feature that distinguishes it from the PER. Taken together, the anatomical connections of the POR are consistent with a role in visuospatial orienting.

The PER receives massive sensory related input and thus emerges as the locus of a convergence of perceptual information. In particular, the mid-rostrocaudal levels of area 36 receive abundant projections from the ventral temporal cortex, and the rostral portion of area 35 is strongly innervated by agranular insular cortex. The PER also receives afferent projections from unimodal sensory association regions of all modalities. The ventral subdivision of the PER (area 35) receives robust olfactory sensory information from the piriform cortex and the subcortical olfactory areas, while the dorsal PER (area 36) receives input from the remaining sensory modalities. Confirming previous studies (Linke, 1999; Doron and Ledoux, 2000; Kimura et al., 2003), the dorsal PER was found to receive a strong direct thalamic projection from auditory-related nuclei. Additionally, the anatomical findings of postrhinal and perirhinal connectivity nicely support a recent study that demonstrated neurons in rostral PER responded only to somatosensory input, while caudal portions of the PER and the POR responded more readily to visual input (Naber et al., 2000). Taken together, these data provide further evidence of polymodal processing in the PER. Indeed, functional studies across evolutionarily advanced species, from rodents to primates, strongly support an essential role for PER in perceptual processing of complex multifeature stimuli (Gaffan et al., 2000; Buckley et al., 2001; Eacott et al., 2001; Bussey et al., 2002; Barense et al., 2005; Lee et al., 2005). The strong PER connections with the amygdala further suggest that it may be involved in affective processing of stimuli that are behaviorally relevant.

As part of the rodent homolog of the primate medial temporal lobe, the connections of the POR and PER with the hippocampal structures have long been a topic of study. The POR provides strong input to the hippocampal system that terminates primarily in the medial entorhinal cortex (Naber et al., 1997; Burwell and Amaral, 1998a). The POR is densely interconnected with the dorsocaudal medial entorhinal area, which was recently reported to have a unique role in spatial functions (Fyhn et al., 2004; Hafting et al., 2005). Entorhinal cells in this region exhibit multipeaked place fields forming a grid that accurately predicts the location of the rat. The resulting allocentric spatial representations may depend on the POR input to the dorsocaudal medial entorhinal area. There are also direct connections with field CA1 of the dorsal hippocampus and with dorsal subiculum (Naber et al., 2001; Kloosterman et al., 2003; Agster, 2007). These connections suggest that visuospatial information is delivered to the hippocampus via a dedicated pathway involving the dorsal subiculum, the POR, and the medial entorhinal cortex. In contrast to the POR, the projections from the PER terminate in the lateral entorhinal cortex within the hippocampal system (Witter et al., 1990, 2000; Naber et al., 1997, 1999; Burwell and Amaral, 1998b). Direct connections between the PER and the subiculum have also been reported (Kosel et al., 1983; Naber et al., 1997, 1999; Kloosterman et al., 2003), but the most abundant hippocampal system connections of the PER are with the lateral entorhinal cortex of the parahippocampal region (Fig. 5B).

The strong connections of the POR and PER with the hippocampal formation and related structures suggests a role in processing spatial information. Experiments conducted in our laboratory, however, indicate that spatial processing functions of the PER and POR are distinct from those of the hippocampus. Perirhinal and postrhinal damage were shown to cause deficits in contextual learning while sparing spatial navigation

in the same animals (Burwell et al., 2004b). Thus, the neural bases of contextual learning can be functionally dissociated from spatial navigation (see also Epstein et al., 1999; Epstein and Kanwisher, 1998).

Because the POR and PER are involved in contextual fear conditioning, the connections of these regions with the amygdala are of interest (Figs. 4 and 5). The amygdala is critical for associative emotional memory (LeDoux, 2000; McGaugh, 2004; Fanselow and Poulos, 2005). The PER and POR are reciprocally connected with the amygdala; however, the amygdala input to the PER is much stronger than that to the POR. Consistent with previous studies, the heaviest PER and POR connections are with the lateral and basolateral nuclei of the amygdala (Shi and Cassell, 1997, 1999; Pitkanen et al., 2000; Pikkarainen and Pitkanen, 2001; Majak and Pitkanen, 2003). The observed deficits in contextual fear conditioning following damage to the hippocampus (Phillips and LeDoux, 1992), the POR (Bucci et al., 2000, 2002), and the PER (Romanski and LeDoux, 1992; Bucci et al., 2000, 2002; Lindquist et al., 2004), are likely influenced by these connections. The POR connections with the amygdala may also support the POR role in attentional orienting (Bucci and Burwell, 2004). Thus based on the anatomical projections and experimental lesion studies, it appears that the PER and POR may interact with structures involved in associative learning about emotional or event-related stimuli and contexts.

In conclusion, the medial temporal lobe has a well documented role in episodic memory. The role of context in episodic memory is not well understood. Moreover, there are open questions about how items to be remembered are identified for further processing by the medial temporal lobe. The available functional and neuroanatomical evidence indicates that the POR is involved in visuospatial orienting and that the PER plays a selective role in processing of multifeature and multimodal stimuli, especially when stimuli are behaviorally relevant.

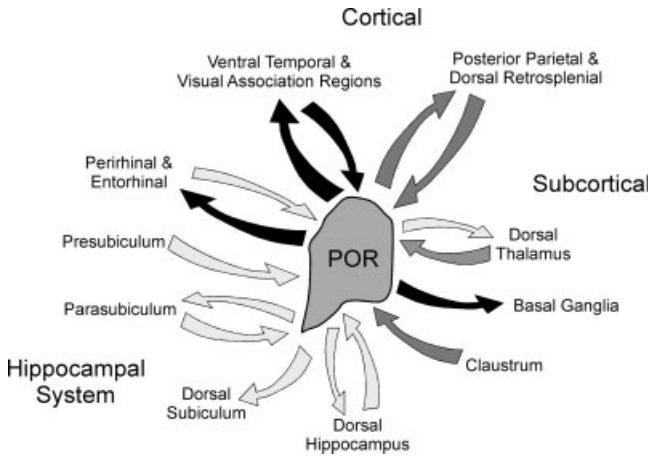

FIGURE 4. Summary of the afferent and efferent connections of the postrhinal cortex (POR). The strongest projections of the POR are reciprocal. Note, strong connections are represented by black arrows, moderate connections are denoted by dark gray arrows, and weak connections are indicated by the light gray arrows.

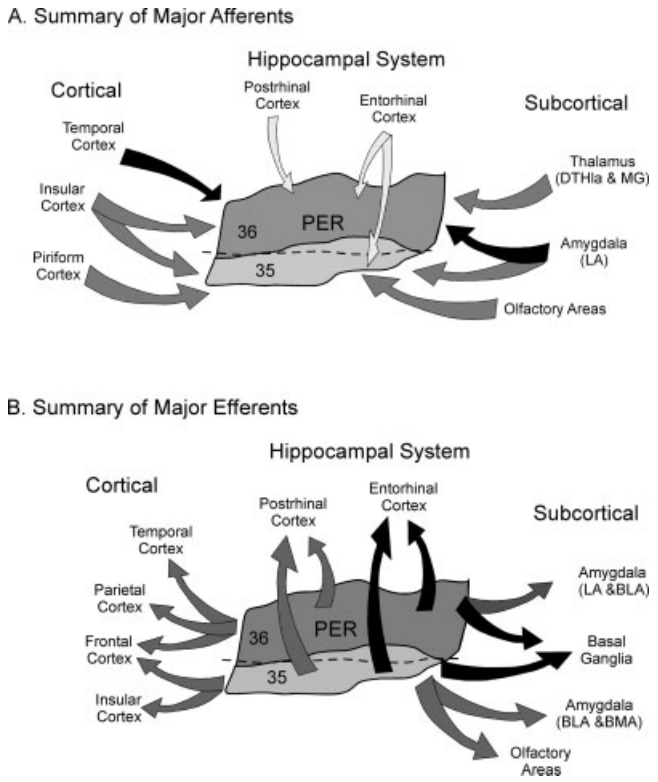

FIGURE 5. Summary of the afferent and efferent connections of areas 35 and 36 of the perirhinal cortex (PER). A: A summary diagram of afferent connections to the PER. B: A summary diagram of efferent connections of the PER. Note, strong connections are represented by black arrows, moderate connections are denoted by dark gray arrows, and weak connections are indicated by the light gray arrows.

Both regions appear to be involved in contextual learning. The anatomical connections are consistent with the hypothesis that the POR monitors the environment for changes and signals other medial temporal structures that the spatial context has changed. The PER may act on the POR signal to encode features of the new context and to evaluate stimuli within the context for behavioral relevance.

REFERENCES

Agster KL. 2007. Structure and function of rodent postrhinal cortex: Comparisons to other cortical regions. Providence: Brown University. 317 p.

Barense MD, Bussey TJ, Lee AC, Rogers TT, Davies RR, Saksida LM, Murray EA, Graham KS. 2005. Functional specialization in the human medial temporal lobe. J Neurosci 25:10239–10246.

Bohbot VD, Allen JJ, Nadel L. 2000. Memory deficits characterized by patterns of lesions to the hippocampus and parahippocampal cortex. Ann N Y Acad Sci 911:355–368.

Brodmann K. 1909. Vergleichende Lokalisationslehre der Grosshirnrinde in ihren Prinzipien dargestellt auf Grund des Zellenbaues. Liepzig: Barth. 1–324p.

Broussard J, Sarter M, Givens B. 2006. Neuronal correlates of signal detection in the posterior parietal cortex of rats performing a sustained attention task. Neuroscience 143:407–417.

Bucci DJ, Burwell RD. 2004. Deficits in attentional orienting following damage to the perirhinal or postrhinal cortices. Behav Neurosci 118:1117–1122.

Bucci DJ, Phillips RG, Burwell RD. 2000. Contributions of postrhinal and perirhinal cortex to contextual information processing. Behav Neurosci 114:882–894.

Bucci DJ, Saddoris MP, Burwell RD. 2002. Contextual fear discrimination is impaired by damage to the postrhinal or perirhinal cortex. Behav Neurosci 116:479–488.

Buckley MJ, Booth MCA, Rolls ET, Gaffan D. 2001. Selective perceptual impairments after perirhinal cortex ablation. J Neurosci 21: 9824–9836.

Burwell RD. 2000. The parahippocampal region: Corticocortical connectivity. Ann N Y Acad Sci 911:25–42.

Burwell RD. 2001. Borders and cytoarchitecture of the perirhinal and postrhinal cortices in the rat. J Comp Neurol 437:17–41.

Burwell RD, Amaral DG. 1998a. Cortical afferents of the perirhinal, postrhinal, and entorhinal cortices of the rat. J Comp Neurol 398:179–205.

Burwell RD, Amaral DG. 1998b. Perirhinal and postrhinal cortices of the rat: Interconnectivity and connections with the entorhinal cortex. J Comp Neurol 391:293–321.

Burwell RD, Hafeman DM. 2003. Positional firing properties of postrhinal cortex neurons. Neuroscience 119:577–588.

Burwell RD, Witter MP, Amaral DG. 1995. Perirhinal and postrhinal cortices of the rat: A review of the neuroanatomical literature and comparison with findings from the monkey brain. Hippocampus 5: 390–408.

Burwell RD, Bucci DJ, Sanborn MR, Jutras MJ. 2004a. Perirhinal and postrhinal contributions to remote memory for context. J Neurosci 24:11023–11028.

Burwell RD, Saddoris MP, Bucci DJ, Wiig KA. 2004b. Corticohippocampal contributions to spatial and contextual learning. J Neurosci 24:3826–3836.

Bussey TJ, Saksida LM, Murray EA. 2002. Perirhinal cortex resolves feature ambiguity in complex visual discriminations. Eur J Neurosci 15:365–374.

Chapin JK, Lin CS. 1984. Mapping the body representation in the SI cortex of anesthetized and awake rats. J Comp Neurol 229:199–213.

Corodimas KP, LeDoux JE. 1995. Disruptive effects of posttraining perirhinal cortex lesions on conditioned fear: Contributions of contextual cues. Behav Neurosci 109:613–619.

Donoghue JP, Wise SP. 1982. The motor cortex of the rat: cytoarchitecture and microstimulation mapping. J Comp Neurol 212:76–88.

Doron NN, Ledoux JE. 2000. Cells in the posterior thalamus project to both amygdala and temporal cortex: A quantitative retrograde double-labeling study in the rat. J Comp Neurol 425:257–274.

Eacott MJ, Machin PE, Gaffan EA. 2001. Elemental and configural visual discrimination learning following lesions to perirhinal cortex in the rat. Behav Brain Res 124:55–70.

Epstein R, Kanwisher N. 1998. A cortical representation of the local visual environment. Nature 392:598–601.

Epstein R, Harris A, Stanley D, Kanwisher N. 1999. The parahippocampal place area: Recognition, navigation, or encoding? Neuron 23:115–125.

Fanselow MS, Poulos AM. 2005. The neuroscience of mammalian associative learning. Annu Rev Psychol 56:207–234.

Fyhn M, Molden S, Witter MP, Moser EI, Moser MB. 2004. Spatial representation in the entorhinal cortex. Science 305:1258–1264.

Gaffan EA, Eacott MJ, Simpson EL. 2000. Perirhinal cortex ablation in rats selectively impairs object identification in a simultaneous visual comparison task. Behav Neurosci 114:18–31.

Haberly LB, Price JL. 1978. Association and commissural fiber systems of the olfactory cortex of the rat. J Comp Neurol 178:711–740.

Hafting T, Fyhn M, Molden S, Moser MB, Moser EI. 2005. Microstructure of a spatial map in the entorhinal cortex. Nature 436: 801–806.

Holscher C, Rolls ET, Xiang J. 2003. Perirhinal cortex neuronal activity related to long-term familiarity memory in the macaque. Eur J Neurosci 18:2037–2046.

Insausti R, Herrero MT, Witter MP. 1997. Entorhinal cortex of the rat: Cytoarchitectonic subdivisions and the origin and distribution of cortical efferents. Hippocampus 7:146–183.

Jones EG. 1985. The Thalamus. New York: Plenum.

Jung MW, Wiener SI, McNaughton BL. 1994. Comparison of spatial firing characteristics of units in dorsal and ventral hippocampus of the rat. J Neurosci 14:7347–7356.

Kimura A, Donishi T, Sakoda T, Hazama M, Tamai Y. 2003. Auditory thalamic nuclei projections to the temporal cortex in the rat. Neuroscience 117:1003–1016.

Kloosterman F, Witter MP, Van Haeften T. 2003. Topographical and laminar organization of subicular projections to the parahippocampal region of the rat. J Comp Neurol 455:156–171.

Kloosterman F, van Haeften T, Lopes da Silva FH. 2004. Two reentrant pathways in the hippocampal-entorhinal system. Hippocampus. 14:1026–1039.

Kosel KC, Van Hoesen GW, Rosene DL. 1983. A direct projection from the perirhinal cortex (area 35) to the subiculum in the rat. Brain Res 269:347–351.

Krettek JE, Price JL. 1977. The cortical projections of the mediodorsal nucleus and adjacent thalamic nuclei in the rat. J Comp Neurol 171:157–191.

Krettek JE, Price JL. 1978. A description of the amygdaloid complex in the rat and cat with observations on intra-amygdaloid axonal connections. J Comp Neurol 178:255–280.

Krieg WJS. 1946a. Connections of the cerebral cortex. I. The albino rat. A. Topography of the cortical areas. J Comp Neurol 84:221–275.

Krieg WJS. 1946b. Connections of the cerebral cortex. I. The albino rat. B. Structure of the cortical areas. J Comp Neurol 84:277–323.

LeDoux JE. 2000. Emotion circuits in the brain. Annu Rev Neurosci 23:155–184.

Lee AC, Bussey TJ, Murray EA, Saksida LM, Epstein RA, Kapur N, Hodges JR, Graham KS. 2005. Perceptual deficits in amnesia: Challenging the medial temporal lobe "mnemonic" view. Neuropsychologia 43:1–11.

Lindquist DH, Jarrard LE, Brown TH. 2004. Perirhinal cortex supports delay fear conditioning to rat ultrasonic social signals. J Neurosci 24:3610–3617.

Linke R. 1999. Organization of projections to temporal cortex originating in the thalamic posterior intralaminar nucleus of the rat. Exp Brain Res 127:314–320.

Liu P, Bilkey DK. 2002. The effects of NMDA lesions centered on the postrhinal cortex on spatial memory tasks in the rat. Behav Neurosci 116:860–873.

Majak K, Pitkanen A. 2003. Projections from the periamygdaloid cortex to the amygdaloid complex, the hippocampal formation, and the parahippocampal region: A PHA-L study in the rat. Hippocampus 13:922–942.

McGaugh JL. 2004. The amygdala modulates the consolidation of memories of emotionally arousing experiences. Annu Rev Neurosci 27:1–28.

Moser E, Moser MB, Andersen P. 1993. Spatial learning impairment parallels the magnitude of dorsal hippocampal lesions, but is hardly present following ventral lesions. J Neurosci 13:3916–3925.

Moser MB, Moser EI, Forrest E, Andersen P, Morris RG. 1995. Spatial learning with a minislab in the dorsal hippocampus. Proc Natl Acad Sci USA 92:9697–9701.

Murray EA, Mishkin M. 1998. Object recognition and location memory in monkeys with excitotoxic lesions of the amygdala and hippocampus. J Neurosci 18:6568–6582.

Murray EA, Baxter MG, Gaffan D. 1998. Monkeys with rhinal cortex damage or neurotoxic hippocampal lesions are impaired on spatial scene learning and object reversals. Behav Neurosc 112:1291–1303.

Murray EA, Bussey TJ, Hampton RR, Saksida LM. 2000. The parahippocampal region and object identification. Ann N Y Acad Sci 911:166–174.

Naber PA, Caballero-Bleda M, Jorritsma-Byham B, Witter MP. 1997. Parallel input to the hippocampal memory system through peri- and postrhinal cortices. Neuroreport 8:2617–2621.

Naber PA, Witter MP, Lopez da Silva FH. 1999. Perirhinal cortex input to the hippocampus in the rat: Evidence for parallel pathways, both direct and indirect. A combined physiological and anatomical study. Eur J Neurosci 11:4119–4133.

Naber PA, Witter MP, Lopes da Silva FH. 2000. Differential distribution of barrel or visual cortex. Evoked responses along the rostrocaudal axis of the peri- and postrhinal cortices. Brain Res 877:298–305.

Naber PA, Witter MP, Lopes da Silva FH. 2001. Evidence for a direct projection from the postrhinal cortex to the subiculum in the rat. Hippocampus 11:105–117.

Norman G, Eacott MJ. 2005. Dissociable effects of lesions to the perirhinal cortex and the postrhinal cortex on memory for context and objects in rats. Behav Neurosci 119:557–566.

Paxinos G, Watson C. 1986. The Rat Brain in Stereotaxic Coordinates. San Diego: Academic Press.

Phillips RG, LeDoux JE. 1992. Differential contribution of amygdala and hippocampus to cued and contextual fear conditioning. Behav Neurosci 106:274–285.

Pikkarainen M, Pitkanen A. 2001. Projections from the lateral, basal and accessory basal nuclei of the amygdala to the perirhinal and postrhinal cortices in rat. Cereb Cortex 11:1064–1082.

Pitkanen A, Pikkarainen M, Nurminen N, Ylinen A. 2000. Reciprocal connections between the amygdala and the hippocampal formation, perirhinal cortex, and postrhinal cortex in rat. A review. Ann N Y Acad Sci 911:369–391.

Posner MI, Petersen SE. 1990. The attention system of the human brain. Annu Rev Neurosci 13:25–42.

Romanski LM, LeDoux JE. 1992. Bilateral destruction of neocortical and perirhinal projection targets of the acoustic thalamus does not disrupt auditory fear conditioning. Neurosci Lett 142:228–232.

Rose M. 1929. Cytoarchitektonischer atlas der Groshirnrinde der Maus. Journal Fur Psychologie und Neurologie 40:1–32.

Scharfman HE, Witter MP, Schwarcz R. 2000. The parahippocampal region. Implications for neurological and psychiatric diseases. Introduction. Ann N Y Acad Sci 911:ix–xiii.

Shapiro ML, Tanila H, Eichenbaum H. 1997. Cues that hippocampal place cells encode: Dynamic and hierarchical representation of local and distal stimuli. Hippocampus 7:624–642.

Shi CJ, Cassell MD. 1997. Cortical, thalamic, and amygdaloid projections of rat temporal cortex. J Comp Neurol 382:153–175.

Shi CJ, Cassell MD. 1999. Perirhinal cortex projections to the amygdaloid complex and hippocampal formation in the rat. J Comp Neurol 406:299–328.

Swanson LW. 1992. Brain Maps: Structure of the Rat Brain, 1st ed. New York: Elsevier.

Swanson LW. 1998. Brain Maps: Structure of the Rat Brain, 2nd ed. New York: Elsevier.

Vaudano E, Legg CR, Glickstein M. 1991. Afferent and efferent connections of temporal association cortex in the rat: A horseradish peroxidase study. Eur J Neurosci 3:317–330.

Vogt BA, Miller MW. 1983. Cortical connections between rat cingulate cortex and visual, motor, and postsubicular cortices. J Comp Neurol 216:192–210.

Von Bonin G, Bailey P. 1947. The Neocortex of Macaca Mulatta. Urbana: University of Illinois Press.

Winters BD, Forwood SE, Cowell RA, Saksida LM, Bussey TJ. 2004. Double dissociation between the effects of peri-postrhinal cortex and hippocampal lesions on tests of object recognition and spatial memory: Heterogeneity of function within the temporal lobe. J Neurosci 24:5901–5908.

Winters BD, Saksida LM, Bussey TJ. 2006. Paradoxical facilitation of object recognition memory after infusion of scopolamine into perirhinal cortex: Implications for cholinergic system function. J Neurosci 26:9520–9529.

Witter MP, Amaral DG. 2004. Hippocampal formation. In: Paxinos G, editor. The Rat Nervous System, 3rd ed. San Diego: Academic Press. pp 635–704.

Witter MP, Room P, Groenewegen HJ, Lohman AH. 1988. Reciprocal connections of the insular and piriform claustrum with limbic cortex: an anatomical study in the cat. Neuroscience 24:519–539.

Witter MP, Ostendorf RH, Groenewegen HJ. 1990. Heterogeneity in the dorsal subiculum of the rat. Distinct neuronal zones project to different cortical and subcortical targets. Eur J Neurosci 2:718–725.

Witter MP, Naber PA, van Haeften T, Machielsen WC, Rombouts SA, Barkhof F, Scheltens P, Lopes da Silva FH. 2000. Cortico-hippocampal communication by way of parallel parahippocampal-subicular pathways. Hippocampus 10:398–410.

Zhu XO, Brown MW. 1995. Changes in neuronal-activity related to the repetition and relative familiarity of visual-stimuli in rhinal and adjacent cortex of the anesthetized rat. Brain Res 689:101–110.

Zhu XO, Brown MW, Aggleton JP. 1995. Neuronal signaling of information important to visual recognition memory in rat rhinal and neighboring cortices. Eur J Neurosci 7:753–765.